1 **Effects of MiR-137 Genetic Risk Score on Brain Volume and Cortical Measures in Patients with Schizophrenia and Controls**

Running title: Effect of MiR-137 PRS on sMRI Measures

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Abstract

Multiple genome-wide association studies of schizophrenia have implicated genetic variants within the gene encoding microRNA-137. As risk variants within or regulated by *MIR137* have been implicated in memory performance, we investigated the additive effects of schizophrenia-associated risk variants in genes empirically regulated by *MIR137* on brain regions associated with memory function. A polygenic risk score (PRS) was calculated (at a p=0.05 threshold), using this empirically regulated *MIR137* gene set, to investigate associations between this PRS and structural brain measures. These measures included total brain volume, cortical thickness, cortical surface area, and hippocampal volume, in a sample of 216 individuals consisting of healthy participants (n= 171) and patients with psychosis (n=45). We did not observe a significant association between *MIR137* PRS and these cortical thickness, surface area or hippocampal volume measures linked to memory function; a significant association between increasing PRS and decreasing total brain volume, independent of diagnosis status (R^2 = 0.008, Beta = -0.09, p = 0.029), was observed. This did not survive correction for multiple testing. In conclusion, our study yielded only suggestive evidence that risk variants interacting with *MIR137* impacts on cortical structure.

Key words: polygene, GWAS, psychosis, total brain volume

Introduction

Genome-wide association studies (GWAS) of schizophrenia (SZ) have so far identified 108 regions of DNA encompassing ~350 genes. A strongly polygenic model of SZ, where the overall influence of many genes of small effect combine to increase an individual's predisposition to SZ has been robustly supported (Purcell et al., 2009). No one 'schizophrenia gene' of large effect has been identified, with the number of genes associated with the disorder increasing as GWAS sample size increases. This interplay of SZ risk genes is important to study, given the polygenic nature of the disorder. To characterise the phenotypic effects of multiple risk variants we and others have used polygenic risk scores calculated for gene sets based on either their involvement in a known biological pathway (Hargreaves et al., 2013), or based on evidence of their being regulated by target risk genes, e.g. *ZNF804A* (Nicodemus et al., 2014); *MIR137* (Cosgrove et al., 2017). In these studies, similar effects on cognitive function have been observed by studying either the risk variant individually or the gene network with which it interacts, although the network based analysis can sometimes explain a slightly higher percentage of variation (Cosgrove et al., 2017).

Genetic variants within the gene for microRNA 137 have been among the most significant findings in multiple GWAS (Ripke et al., 2013, The Schizophrenia Psychiatric GWAS Consortium, 2011, Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In the 2011 PGC GWAS, the SNP rs1702294 was the strongest new finding; and in 2014, rs1625579 was the third most highly SZ-associated SNP, both sited in the region of *MIR137* (r^2 = 0.99 with rs1702294). Evidence also suggests that *MIR137* may not uniquely be associated with SZ (Hamshere et al., 2013). There is a strong genetic overlap between SZ and bipolar disorder (Cross-Disorder Group of the Psychiatric Genomics et al., 2013,

Moskvina et al., 2008), even leading to some questions about the diagnostic boundaries between these disorders (Lichtenstein et al., 2009). *In silico* and *in vitro* studies looking at the downstream effects of microRNA-137 have predicted or shown it to impact on the regulation of other genes linked to psychosis (Hill et al., 2014, Collins et al., 2014, Wright et al., 2013). In a study performed to characterise the regulatory effects of miR-137, under-expression of miR-137 led to a general upregulation of many genes, with the opposite shown in overexpression (Olde Loohuis et al., 2017). Risk alleles of four SZ-associated SNPs in the region of *MIR137* (rs1198588, rs1625579, rs2660304 and rs2802535) have been associated with downregulation of miR-137, specific to neuronal cells (Siegert et al., 2015).

MicroRNAs are responsible for the post-translational modification of RNA, altering the quantity of the gene products produced, which has implications for cell function (Yin et al., 2014). *MIR137* functions as a 'fine-tuning' agent for synaptic pruning and dendritic arborisation in neural cells and has been associated with, in addition to SZ, altered cognitive function (Kuswanto et al., 2015, Cummings et al., 2013, Green et al., 2013). Patients with SZ experience symptoms of cognitive dysfunction, which have been identified as being one of the largest obstacles to improving SZ patients' functional outcome (Green et al., 2015). *MIR137* regulates processes that are potentially involved with cognitive dysfunction, in part by acting as a hippocampal gene network node, co-ordinating the expression of genes relating to nervous system function and development (Olde Loohuis et al., 2017). The risk alleles of each of the rs1702294 (C) and rs1625579 (T) SNPs have been linked to poorer scores on neuropsychological tests of memory performance (Cummings et al., 2013, Cosgrove et al., 2017). Furthermore, we previously observed an association between a *MIR137* PRS and memory scores, and between *MIR137* PRS and altered neural connectivity during performance of a fMRI working memory task (Cosgrove et al., 2017). There are conflicting

reports of the effect of the rs1625579 SNP on brain volume (Rose et al., 2014, Lett et al., 2013, Cousijn et al., 2014, Patel et al., 2015); however, to date, the effect of an empirically derived miR-137 regulated gene score on structural brain measures has not been established. Such investigations into potential associations between genetic pathways and brain-based correlates of cognitive phenotypes may assist in elucidating pathophysiological mechanisms that act as contributing factors to these cognitive deficits.

Given the link between *MIR137* and cognition, particularly memory function, the purpose of this study is to investigate the effects of a *MIR137* genetic risk score on measures of cortical thickness, cortical area, hippocampal volume and total brain volume in a sample of healthy participants and patients with psychosis. We hypothesise that participants carrying a higher *MIR137* polygenic risk burden, i.e. higher PRS, will show decreased cortical thickness, cortical area, hippocampal volume and total brain volume in comparison to those with a lower PRS.

Subjects and Methods

Participants

Participants were recruited in Dublin, patients through outpatient clinics (35 patients with SZ, 8 with schizoaffective disorder and 2 with bipolar disorder) and healthy participants through local media advertising. All participants were Irish, i.e. all four grandparents Irish. All participants were screened for MRI safety criteria, and provided written informed consent in accordance with the guidelines of the local ethics committee (St. James' Hospital). Healthy participants (n=171) age 18-65 were included if they had no history of psychiatric illness, head injury, or drug abuse. Healthy participant sampling at the Dublin site included individuals involved in the Trinity College Biobank project, described in (Rose et al., 2012). All patients (n=45) were chronic, but stable, medicated outpatients, with a confirmed a DSM-IV diagnosis. Demographic and other additional information is presented in **Table 1**.

Magnetic Resonance Imaging (MRI)

Structural MRI sequences were acquired on a Philips Intera Achieva 3T MR system, with whole-brain imaging consisting of a T1-weighted image (180 slices; duration 6 min) using a TFE gradient echo pulse sequence, with a slice thickness of 0.9 mm, and 230 × 230 FOV.

FreeSurfer MRI Processing

Structural MRI images were reconstructed into a three dimensional model of the cortical thickness measurements using FreeSurfer v5.3 which allows for cortical thickness and surface area measurements at numerous locations (vertices) across the surface (Dale et al.,

1999). Processed images were prepared for analysis using the ENIGMA protocol. Briefly, the automated -recon-all function was performed on each scan. Each image underwent motion correction, intensity normalisation, transformation to Talairach space and skull stripping. Mathematical outliers were detected by using R software as per the ENIGMA protocol. In addition to this, each output was visually inspected for T1 quality (artefacts, contrast, resolution, intensity) and to ensure adequate reconstruction. Manual edits to pial surfaces and white matter intensity were carried out where necessary by trained researchers (DC, JH).

Cortical reconstruction, parcellation and segmentation of T1 images were performed using the FreeSurfer 5.3 pipeline, available online. A full description of the FreeSurfer reconstruction process can be found by Dale et al. 1999 (Dale et al., 1999) and Fischl et al. 1999 (Fischl et al., 1999a). The MRI image is 3D rendered into a volume from the MRI into 256 coronal slices (1mm x 1mm x 1mm voxels) and undergoes automated transformation to the Talairach atlas (Talairach and Tournoux, 1988). Intensity normalization is then performed (Sled et al., 1998) to correct non-uniformity in the image due to radiofrequency field. The variation in white matter intensity is then used to estimate the bias field across the entire volume, and the effect of bias field removed by dividing the intensity at each voxel by the estimated bias field at that location. Following this, skull stripping (using a method combining watershed algorithms and deformable surface models) removes the non-brain tissue such as scalp, skull and neck tissue, extracting an initial brain volume (Ségonne et al., 2004). The grey/white matter boundary is estimated by classifying all white matter voxels in an MRI volume, and cerebral white matter segmentation is performed (Fischl and Dale, 2000), deforming this representation of the grey/white boundary outward to the pial surface (Fischl et al., 2001). The WM volume is tiled with a triangular tessellation on each hemisphere to generate an initial surface. The surface deformation follows intensity gradients between white and gray matter, placing the grey/white matter or cerebrospinal fluid borders

at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale and Sereno, 1993, Dale et al., 1999, Fischl and Dale, 2000). The average of the distance from the WM surface to the closest point on the pial surface and from that point back to the closest point on the WM surface gives us the thickness at each location of cortex (Fischl and Dale, 2000). The inflation of the cortical surface is performed so that activity occurring inside sulci may be easily visualized (Fischl et al., 1999b, Fischl et al., 1999a) and each location on the cortical surface is assigned a neuroanatomical label (34 gyral based regions) based on probabilistic information estimated from a manually labelled training set, and also scan-specific measured values (Fischl et al., 2004b, Desikan et al., 2006). Segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) is performed (Fischl et al., 2002, Fischl et al., 2004a).

Using the ENIGMA protocol for the analysis of mean cortical thickness and surface area data within FreeSurfer ROIs, values for surface area and thickness were extracted. Following this, outliers were identified using R. MATLAB was used to plot cortical surface segmentations directly on each participant's scan and collate snapshots of these into a webpage for visual inspection (the internal surface QC method). The ENIGMA External QC method was performed to check cortical labels and anatomical boundaries. Furthermore, images underwent a thorough visual inspection of each image slice in the coronal, sagittal and axial planes using Freeview.

>>Table 1<<

The automatic segmentation tool Volbrain was used for estimation of hippocampal volume because it is the most accurate method to segment the hippocampus, according to the European Alzheimer's Disease Consortium harmonised hippocampus segmentation protocol, which compares results from software with results from expert manual tracing. This system was used for hippocampal reconstruction as it has been shown that other imaging segmentation software, including FreeSurfer, can overestimate subcortical structures (Manjón and Coupé, 2016). Further information on sMRI processing is available in **Appendix 1.**

VolBrain

The VolBrain pipeline is based on a library of manually labelled templates, constructed from publically available databases: 30 healthy adults, 10 patients with Alzheimer's disease, and 10 infant cases. The pipeline is a set of processing tasks that aims to improve image quality and intensity, and set images into a specific geometric space. Automatic pre-processing of T1-weighted images using the following steps is carried out: denoising and enhancement image quality, inhomogeneity correction, MNI space registration, fine inhomogeneity correction, intensity normalisation, non-local intracranial cavity extraction (white matter, gray matter, and cerebrospinal fluid), tissue classification, non-local hemisphere segmentation (splits brain into five: right and left cerebrum/cerebellum, and brainstem), and non-local subcortical structure segmentation. A more detailed description by Manjón and Coupé (2016) is available.

Genotyping

Genotyping was conducted on DNA samples that were extracted from whole blood or saliva. Samples were genotyped using either Affymetrix 6.0 chip (Santa Clara, CA, USA), as part of the WTCCC2 (Irish Schizophrenia Genomics Consortium and the Wellcome Trust Case Control Consortium, 2012), or Illumina HumanCoreExome chip Illumina (Cardiff sample; San Diego, CA) with full GWAS data available for all participants. Imputation was carried out on these data sets separately using 1000 Genomes Phase I integrated haplotypes (Dec 2013 release) and IMPUTE2 to give ~ 10 million SNPs genome-wide per sample.

Polygene Score

We constructed the *MIR137* PRS based on a set of 1991 genes affected by the up- and downregulation of *MIR137* in human neural progenitor cells (Hill et al., 2014). Of these, 1386 genes that were unambiguously mapped to autosomes were used to generate the PRS (**Supplementary Table 1**). First, the genetic coordinates (+/- 20kb) of these genes were identified (Kent et al., 2002), UCSC hg19 Feb 2009 release. SNPs within these regions were then extracted from our Irish GWAS samples (WTCCC2 and Cardiff; 208,040 and 194,123, respectively). PLINK v1.07 software (Purcell et al., 2007) was used to perform quality control on data from each sample (Affymetrix 6.0 and Illumina HumanCoreExome) separately: SNPs were excluded from further analysis if there was missing genotype data for >10%, Hardy-Weinberg equilibrium < 1×10^{-5}, or MAF < 1%. Next, the lists of SNPs that passed QC for each sample were joined, providing a SNP list common to each sample (n=185,259 SNPs) regardless of genotyping platform used. This list of common SNPs was used in further analysis. LD clumping was performed separately in each sample using PLINK (–clump, r = 0.25, distance = 250kb) due to slightly differing LD, giving a list of 2,214 (Cardiff Illumina sample) and 2,235 (WTCCC2 Affymetrix sample) SNPs. Following this,

the PRS was generated for each sample using the LD clump results from the Affymetrix sample. The PRS did not significantly change based on which LD clump results were used: when the PRS was generated using the Illumina sample LD clump values, the results were highly correlated (r=0.9, $p<0.001$). The PRS risk threshold defined here was $p=0.05$. Previous studies have used multiple PRS thresholds to investigate associations, however, in prior work we have observed a threshold of $p=0.05$ to be the most informative (Cosgrove et al., 2017). Finally, each participant was given a PRS based number of risk alleles that they carried for each SNP, with alleles weighted by their effect size from the PGC2 GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) (using the –score function in PLINK). These effects sizes were taken from a meta-analysis of the PGC2 sample minus all Irish samples to make sure that the discovery and target samples used here were independent.

Statistical Analysis

Age, gender and intracranial volume were used as covariates in all analyses. Whole brain, vertex based analysis was carried out to estimate any effect of PRS on cortical thickness or cortical surface area of the left or right hemispheres. This was performed using the general linear model in QDEC (FreeSurfer), corrected for false discovery rate <0.05. Analysis of *MIR137* PRS effect on total brain volume and hippocampal volume was performed in SPSS version 23 (IBM Corp, 2015), with moderation analyses carried out using the PROCESS macro for SPSS.

Results

Participant demographics, brain volume measures and *MIR137* PRS values are displayed in **table 1**. Reflecting the fact that healthy participants were recruited separately from patients rather than as a 'control' group, patients were on average older and mostly male. As expected, patients had a significantly higher *MIR137* PRS ($t_{(214)} = -3.16$, $p < 0.05$). The patient groups were also observed to show lower hippocampal volume ($t_{(214)} = 2.12$, $p < 0.05$) compared to healthy participants. Brain volume did not show statistically significant differences between cases and controls, although trend level differences for patients to show lower brain volumes were observed ($t_{(214)} = 1.82$, $p = 0.071$, **table 1**).

MIR137 PRS & Total Brain Volume

In the full sample of patients and controls, an effect of PRS on total brain volume was observed ($R^2 = 0.008$, Beta = -0.09, $p = 0.029$, t**able 2**). After correcting for the four sets of analysis carried out however, this finding was no longer significant. As a *post hoc* analysis a moderation analysis was carried out using diagnosis (healthy participants vs. patients with psychosis) as the moderator to determine whether this trend level effect was influenced by diagnosis. After co-varying for the effects of age, gender and intracranial volume, no significant moderating effects of diagnosis on the relationship between *MIR137* PRS and brain volume ($p = 0.96$, $R^2 = 0.00$) were observed, suggesting that the relationship between *MIR137* and brain volume was comparable in both groups. An additional analysis was performed to investigate the effect of medication on this nominally significant finding. Most patients in our sample were medicated, with current medication dose in chlorpromazine equivalent (CPZE) available for 36 out of the 45 patients; healthy participants were not taking any antipsychotic medication. When the analysis was run again including CPZE as well as

age, gender and ICV, the strength of association observed between increasing *MIR137* PRS and lower brain volume decreased ($R^2 = 0.005$, Beta = -0.072, $p = 0.087$).

MIR137 PRS & Cortical Thickness and Surface Area

No effect of *MIR137* PRS was observed on either cortical thickness or surface area (corrected for false discovery rate <0.05).

MIR137 PRS & Hippocampal Volume

No effect of *MIR137* PRS on hippocampal volume, estimated from segmentation results from VolBrain was observed (**Table 2)**.

>>Table 2<<

Discussion

In this study we sought to determine the effect of a SZ-associated, empirically derived, miR-137 regulated gene score on measures of cortical thickness and area, hippocampal volume, and total brain volume. Given the previous reported associations between *MIR137* PRS and cognitive performance, most notably with lower scores on neuropsychological measures of memory function, we hypothesised that a higher PRS would be associated with a decreased cortical thickness and surface area, decreased hippocampal volume and lower total brain volume. No significant association between either cortical thickness or surface area or hippocampal measures and *MIR137* PRS were observed. While association between PRS and total brain volume was nominally significant, when medication (CPZE) was included as an additional covariate in the analysis, this nominally significant association between increasing *MIR137* PRS and decreasing brain volume was no longer significant.

To the best of our knowledge, no study has examined the effect of a *MIR137* PRS score on cortical thickness, shape or volume. Previous imaging studies have investigated the effect of the SZ-associated *MIR137* SNP rs1625579 on brain structure, activation and connectivity and have provided mixed results: this might partly be expected based on the study samples (inclusion of healthy participants only, compared to those looking at patient populations), as well as different regions of interest studied, and the different fMRI tasks used, if any. The first study to investigate the effects of rs1625579 on brain structure by Lett et al. (2013) showed significantly increased ventricle volume in both SZ patients (n=92) and controls (n=121) homozygous for the risk (TT) allele, processed using tools from the FMRIB Software Library (FIRST). In addition, decreased hippocampal volume was observed, but only in patients homozygous for the risk (TT) allele (Lett et al., 2013). Two subsequent structural neuroimaging studies however did not replicate these findings. Cousijn et al. (2014) analysed a large sample of healthy participants (n=1300), also using FIRST. No effects of

rs1625579 genotype on total brain, grey matter, white matter, or hippocampal volumes were observed. Rose et al. (2014) Rose et al. (2014) also looked at the effect of the same *MIR137* rs1625579 risk variant in a voxel-based morphometry study (using SPM) of grey and white matter volume in patients with SZ (n=163) and healthy participants (n=150) and did not observe any significant effects. Similarly, no significant association between genotype and volume of any subcortical regions analysed (using FIRST) was identified in this study, including the hippocampus. The results of the present study are comparable to the results of the larger two of the three studies in terms of the lack of effect of rs1625579 on hippocampal volume. Furthermore, in one of these larger studies, an association between the rs1625579 risk allele and increased ventricle size was reported (Lett et al., 2013). As ventricle size and total brain volume are inversely correlated (Horga et al., 2011), this increased ventricular volume association may be comparable to the link between decreased total brain volume and PRS in the present study. A final structural MRI study reported by Patel et al. (2015) examined the effect of rs1625579 genotype on subcortical and callosal volumes and reported evidence of an association between the risk (G) allele and decreased corpus callosum volume in SZ patients only (n=362) compared to controls (n=490). We did not examine this measure in our sample, although potentially a decrease in corpus callosum volume may contribute to the decrease in overall brain volume reported here.

In this study, we selected only one threshold of polygene score for investigation to limit the multiple testing burden, but is possible that different score thresholds would yield different results. This was not the case in our previous analyses of the cognitive effects of the *MIR137* PRS however, where similar effects were observed across three thresholds analysed ($p=10^{-5}$, $p=0.05$, $p=0.5$), but most strongly at the $p=0.05$ threshold (Cosgrove et al., 2017), which was the threshold used in this study.

An endophenotypic approach was employed here, i.e. characterising the effects of SZ-associated variants on cortical metrices rather than disease or clinical symptoms (Gottesman and Gould, 2003). The selection of a robust sMRI phenotype to investigate genetic effects is one of the strengths of this study. Total cortical surface area and average cortical thickness are both highly heritable (Panizzon et al., 2009), as is total brain volume (Hulshoff Pol et al., 2002). As surface area and thickness are genetically uncorrelated metrics, these were both investigated (Winkler et al., 2010, Tandon et al., 2016). It has been suggested that cortical thickness is of greater aetiological interest than volume or surface area measures due to the proposed neurodevelopmental mechanisms thought to contribute to SZ and cognitive deficits (Geisler et al., 2015), although no association was observed here between either measure and the *MIR137* PRS. In a meta-analysis comparing cognitive and brain imaging phenotypes, results suggested that SZ variants have greater penetrance on measures of brain structure than other phenotypic measures, such as cognitive performance (Rose and Donohoe, 2013).

The lack of effect of the *MIR137* PRS on any specific cortical region or on the hippocampus and the small effect observed for total brain volume (although not significant after either multiple testing correction, or correction for medication effects) may imply a subtle effect of *MIR137* and its interacting network on more widespread neurological structure, as opposed to being specific to memory-related components. A role of *MIR137* in influencing brain microstructure has previously been established: it has an important role in regulation of target genes linked with neural stem cell proliferation and differentiation during neural development (Mahmoudi and Cairns, 2017). Its role beyond this in terms of how these molecular and cellular effects of *MIR137* itself and the whole *MIR137* network impact brain macrostructure is yet to be defined; however, multiple studies provide evidence that *MIR137* may exert some effect through influence of rs1625579 risk (T) genotype on functional connectivity and neural activation (Mothersill et al., 2013, Liu et al., 2014, Whalley et al., 2012, van Erp et al., 2014).

Due to the extensive regulation of other genes by miRNAs, the dysregulation of even one of these may confer a large polygenic effect. In addition to this, there is evidence that *MIR137* also regulates other genes that harbour SZ-associated variants such as *ZNF804A, TCF4, CACNA1C, CSMD1, C10orf26* (Kim et al., 2012, Wright et al., 2013, Guan et al., 2014, Kwon et al., 2013). These convergent pathways linked by *MIR137* may contribute to SZ: previous pathway analysis of miR-137 targets implicated several aspects of nervous system function and development associated with SZ, such as ephrin receptor signalling, axonal guidance signalling and long term potentiation (Wright et al., 2013).

In this study, our sample is comparable, in terms of sample size, with the other studies discussed that investigated the effects of rs1625579 on cortical structures and total brain or hippocampal volumes. Other studies reporting on effects of polygene scores on brain measures include a range of sample sizes. Neilson et al. (2016) reported an association between a SZ polygenic risk score on cortical thinning in patients based on a small sample of 46 patients and 33 controls. Studies such as this with smaller sample sizes report positive associations, however, the replicability of some findings in these smaller study sizes have been questioned (Button et al., 2013). Van der Auwera et al. (2015) observed no effect of a SZ PRS on various structural measures in a large sample of 1,470 healthy participants. Further studies are required to determine if the *MIR137* PRS effects on cortical and hippocampal measures reported here are truly non-significant or whether the uncorrected total brain volume finding may have underestimated an actual effect.

One limitation of this study is that most of our sample was made up of healthy participants. If a potential diagnosis-specific effect was to be identified, a larger patient group would likely be required. As this is the first study to characterise the effect of polygene score on brain structure measures, replication in a different sample is required to further support these findings, preferably in a larger patient population in order to determine whether or not there

are specific disease related consequences of carrying a higher burden of SZ-risk variants in this *MIR137* pathway. In addition, a potential limitation in all imaging studies is that different types of software are used to reconstruct T1 images that can estimate brain volumes differently based on the algorithms used, as well as different QC methodologies. No MDS components were included in the PRS analyses here as the Irish GWAS sample used in the study indicated that the sample was homogeneous. However, it may still be possible that some population stratification effects were present in this sample.

In conclusion, we have not shown evidence of any association between *MIR137* PRS and specific cortical correlates of memory. An association between increasing PRS and decreasing total brain volume however was identified. Further studies with larger sample sizes that include more SZ patients would help clarify the dissociable effects of this microRNA on measures of cognitive function compared to effects in controls. Additional investigations into this miRNA pathway may provide new lines of research to explore in terms of developing a biomarker or therapeutic strategy for SZ.

Acknowledgements

We wish to thank all patients and their support staff, and all healthy volunteers for participating in the data collection on which this manuscript is based. Recruitment and genotyping was supported by Science Foundation Ireland (SFI) (grants 12.IP.1359 and 08/IN.1/B1916) and the Wellcome Trust Case Control Consortium 2 project (grant 085475 /B/08/Z) and the Wellcome Trust (grants 072894/Z/03/Z, 090532/Z/09/Z, and 075491/Z/04/B).

The Wellcome Trust Case Control Consortium 2 investigators include: Peter Donnelly, Lesley Bates, Ines Barroso, Jenefer M. Blackwell, Elvira Bramon, Matthew A. Brown, Juan P. Casas, Aiden Corvin, Panos Deloukas, Audrey Duncanson, Janusz Jankowski, Hugh S. Markus, Christopher G. Mathew, Colin N. A. Palmer, Robert Plomin, Anna Rautanen, Stephen J. Sawcer, Richard C. Trembath, Ananth C. Viswanathan, Nicholas W.Wood, Chris C. A. Spencer, Gavin Band, Céline Bellenguez, Colin Freeman, Garrett Hellenthal, Eleni Giannoulatou, Lucinda Hopkins, Matti Pirinen, Richard Pearson, Amy Strange, Zhan Su, Damjan Vukcevic, Cordelia Langford, Sarah E. Hunt, Sarah Edkins, Rhian Gwilliam, Hannah Blackburn, Suzannah J. Bumpstead, Serge Dronov, Matthew Gillman, Emma Gray, Naomi Hammond, Alagurevathi Jayakumar, Owen T. McCann, Jennifer Liddle, Simon C. Potter, Radhi Ravindrarajah, Michelle Ricketts, Matthew Waller, Paul Weston, Sara Widaa, and Pamela Whittaker.

Conflict of Interest

The authors declare no conflict of interest specific to this work.

Web Resources

UCSC: http://genome.ucsc.edu

ENIGMA: http://enigma.usc.edu/

FreeSurfer: http://surfer.nmr.mgh.harvard.edu

VolBrain: http://volbrain.upv.es

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Tables

Table 1. Participant demographics, brain volume measures and *MIR137* genetic risk score (PRS).

	Healthy Participants	**Patients**	**t**	**df**	**p**
n	171	45	-	-	-
Age	28.57 (10.06)	41.73 (9.77)	-7.85	214	<0.001
Female %	56.14	29.55	3.32	214	<0.05
Education Years	17.10 (3.16)	14.15 (3.95)	4.58	132	<0.001
***MIR137* PRS**	-0.00201 (0.0003)	-0.00185 (0.0003)	-3.16	214	<0.05
***MIR137* PRS (standardised z score)**	-0.11 (0.98)	0.41 (0.99)	-3.16	214	<0.05
Brain Volume (cm3)	11579.45 (1229.44)	11206.31 (1209.52)	1.82	214	0.071
Hippocampal Volume (cm3)	7.88 (0.85)	7.58 (0.87)	2.12	214	<0.05

Table 2. Effect of *MIR137* PRS (standardised z-score) on hippocampal and total brain volume (age, gender, ICV as covariates).

Measure	**B**	**SE B**	**Beta**	R^2	**p**
Hippocampal Volume (cm3)	0.032	0.044	0.037	0.001	0.472
Brain Volume (cm3)	-111.96	50.77	-0.091	0.008	0.029*

Supplementary File 1 - sMRI Processing and QC

FreeSurfer MRI Processing

Cortical reconstruction, parcellation and segmentation of T1 images were performed using the FreeSurfer 5.3 pipeline, available online (http://surfer.nmr.mgh.harvard.edu/). A full description of the FreeSurfer reconstruction process can be found by Dale et al. (1999) and Fischl et al. (1999a). The MRI image is 3D rendered into a volume from the MRI into 256 coronal slices (1mm x 1mm x 1mm voxels) and undergoes automated transformation to the Talairach atlas (Talairach and Tournoux, 1988). Intensity normalization is then performed (Sled et al., 1998) to correct non-uniformity in the image due to radiofrequency field. The variation in white matter intensity is then used to estimate the bias field across the entire volume, and the effect of bias field removed by dividing the intensity at each voxel by the estimated bias field at that location. Following this, skull stripping (using a method combining watershed algorithms and deformable surface models) removes the non-brain tissue such as scalp, skull and neck tissue, extracting an initial brain volume (Ségonne et al., 2004). The grey/white matter boundary is estimated by classifying all white matter voxels in an MRI volume, and cerebral white matter segmentation is performed (Fischl and Dale, 2000), deforming this representation of the grey/white boundary outward to the pial surface (Fischl et al., 2001). The WM volume is tiled with a triangular tessellation on each hemisphere to generate an initial surface. The surface deformation follows intensity gradients between white and gray matter, placing the grey/white matter or cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale and Sereno, 1993, Dale et al., 1999, Fischl and Dale, 2000). The average of the distance from the WM surface to the closest point on the pial surface and from that point back to the closest point on the WM surface gives us the thickness at each location of cortex (Fischl and Dale, 2000). The inflation of the cortical surface is performed so that activity

occurring inside sulci may be easily visualized (Fischl et al., 1999b, Fischl et al., 1999a) and each location on the cortical surface is assigned a neuroanatomical label (34 gyral based regions) based on probabilistic information estimated from a manually labelled training set, and also scan-specific measured values (Fischl et al., 2004b, Desikan et al., 2006). Segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) is performed (Fischl et al., 2002, Fischl et al., 2004a).

Using the ENIGMA protocol for the analysis of mean cortical thickness and surface area data within FreeSurfer ROIs, values for surface area and thickness were extracted. Following this, outliers were identified using R (https://www.r-project.org/). This involves running an R script (http://enigma.ini.usc.edu/wp-content/uploads/CORTEX/outliers.R) to identify any images that have outlier values in any of the 73 cortical measures extracted from FreeSurfer. In this script, outliers are defined as any data points that are more than 1.5 times the inter-quartile range before quartile 1 or after quartile 3 (z scores equivalent to -2.68 or greater than 2.68). Observation of outlier values does not exclude these images from all further analysis automatically, but rather indicates that further inspection to verify image quality is required. Visual inspection is performed on any outlying regions, e.g. where the region may have been poorly segmented by the software. MATLAB was used to plot cortical surface segmentations directly on each participant's scan and collate snapshots of these into a webpage for visual inspection (the internal surface QC method). The ENIGMA External QC method was performed to check cortical labels and anatomical boundaries. Furthermore, images underwent a thorough visual inspection of each image slice in the coronal, sagittal and axial planes using Freeview. The ENIGMA Cortical Quality Control Protocol for QC of images was followed (http://enigma.ini.usc.edu/protocols/imaging-protocols/). While a number of outliers were identified in our sample, there were no more than two outliers/regions identified

for any one image. These were inspected visually and were not found to be visually abnormal; thus were kept in the analysis. One or two outlying regions are unlikely to bias a whole-hemisphere vertex based analysis. Based on this protocol, after QC, no scans met the criteria for exclusion.

VolBrain

The VolBrain pipeline is based on a library of manually labelled templates, constructed from publically available databases: 30 healthy adults, 10 patients with Alzheimer's disease, and 10 infant cases. The pipeline is a set of processing tasks that aims to improve image quality and intensity, and set images into a specific geometric space. Automatic pre-processing of T1-weighted images using the following steps is carried out: denoising and enhancement image quality, inhomogeneity correction, MNI space registration, fine inhomogeneity correction, intensity normalisation, non-local intracranial cavity extraction (WM, GM and CSF), tissue classification, non-local hemisphere segmentation (splits brain into five: right and left cerebrum/cerebellum, and brainstem), and non-local subcortical structure segmentation. A more detailed description by Manjón and Coupé (2016) is available.

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Chromosome	Start	Stop	Gene
1	1017178	1051756	C1orf159
1	1152268	1167467	SDF4
1	1477033	1510282	SSU72
1	2115879	2144179	C1orf86
1	6475272	6484744	HES2
1	9789059	9884570	CLSTN1
1	9789059	9884570	CLSTN1
1	9982148	10003480	LZIC
1	11734517	11751698	MAD2L2
1	15479008	15546994	TMEM51
1	17345197	17380685	SDHB
1	19197904	19229313	ALDH4A1
1	20439123	20446079	PLA2G2D
1	20808864	20812748	CAMK2N1
1	21543720	21672054	ECE1
1	22889984	22930107	EPHA8
1	23037243	23241843	EPHB2
1	23635933	23671163	HNRNPR
1	23685921	23696377	ZNF436
1	24969574	24999792	SRRM1
1	25548747	25559033	SYF2
1	25943939	26111278	MAN1C1
1	28099674	28150983	STX12
1	28526769	28559562	DNAJC8
1	32372002	32404008	PTP4A2
1	33116729	33151832	RBBP4
1	33473521	33502532	AK2
1	36621731	36646470	MAP7D1
1	38022500	38032478	DNALI1
1	38181626	38230844	EPHA10
1	40204497	40229606	PPIE
1	41326708	41328038	CITED4
1	41492851	41707835	SCMH1
1	41827308	41849283	FOXO6
1	43148040	43168044	YBX1
1	44398972	44402932	ARTN
1	44412458	44433714	IPO13
1	44435633	44439063	DPH2
1	46640729	46651654	TSPAN1
1	46769304	46782468	UQCRH
1	47100691	47134119	ATPAF1
1	47799449	47844531	CMPK1
1	48761024	48937896	SPATA6
1	50906915	51425956	FAF1
1	51434347	51440329	CDKN2C
1	52254844	52344629	NRD1
1	52497757	52499492	KTI12
1	52870199	52884012	PRPF38A
1	54411979	54433861	LRRC42
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1	59246443	59249805	JUN
1	62146698	62191115	TM2D1
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1	64058927	64125936	PGM1
1	65298886	65432613	JAK1
1	68150840	68154041	GADD45A
1	68894487	68915662	RPE65
1	77333106	77533243	ST6GALNAC5
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2	44395964	44471590	PPM1B
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2	46808393	46844271	PIGF
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2	56093077	56151318	EFEMP1
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2	64119260	64246546	VPS54
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2	65215559	65251019	SLC1A4
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2	75059762	75120501	HK2
2	86426458	86440933	MRPL35
2	86441096	86565226	REEP1
2	96068419	96082377	FAHD2A
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3	196769411	197026191	DLG1
3	197476404	197511337	FYTTD1
4	666205	668147	ATP5I
4	669697	675842	MYL5
4	1004692	1020706	FGFRL1
4	1004692	1020706	FGFRL1
4	1283622	1333945	MAEA
4	2043700	2045717	C4orf48
4	6641798	6644492	MRFAP1
4	6641798	6644492	MRFAP1
4	8951457	8952147	LOC650293
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4	20702016	20730000	PACRGL
4	25378828	25420140	ANAPC4
4	39046288	39127873	KLHL5
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4	56294048	56413096	CLOCK

4	57276662	57327554	PAICS
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4	71570627	71674356	RUFY3
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4	76942249	76944709	CXCL10
4	77035792	77069688	NUP54
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4	99391498	99579832	TSPAN5
4	100737937	100791367	DAPP1
4	110736646	110745913	GAR1
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4	113434652	113437348	NEUROG2
4	114372168	114683689	CAMK2D
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4	122745464	122791672	BBS7
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4	128982401	129144106	LARP1B
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4	145567128	145662562	HHIP
4	146540520	146581207	MMAA
4	150999406	151178629	DCLK2
4	151185791	151936899	LRBA
4	154265781	154336267	MND1
4	157997257	158093271	GLRB
4	159587807	159593427	C4orf46
4	169137422	169239978	DDX60
4	169418195	169849628	PALLD
4	177241070	177253416	SPCS3
4	184426200	184433442	ING2
4	189060578	189068669	TRIML1
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5	16661996	16936405	MYO10
5	31532353	31555185	C5orf22
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5	32354436	32444864	ZFR
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5	37291715	37371248	NUP155
5	40831410	40835407	RPL37
5	52285136	52390629	ITGA2
5	64885487	64920207	TRIM23
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5	70883095	70954553	MCCC2
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5	72794230	72801468	BTF3
5	76248660	76265319	CRHBP
5	78985639	79096069	CMYA5
5	79922025	79950820	DHFR
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5	79950447	80172654	MSH3
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5	86687290	86708870	CCNH
5	95997721	96110407	CAST
5	102201507	102366829	PAM
5	102594422	102614381	C5orf30
5	110427850	110466220	WDR36
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5	138609421	138667386	MATR3
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5	140855549	140892566	PCDHGC3
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5	145826853	145891091	TCERG1
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5	148737550	148749241	PCYOX1L
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5	172410743	172461920	ATP6V0E1
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5	176732481	176741116	MXD3
5	176784684	176799619	RGS14
5	176883593	176900714	DBN1
5	176910375	176924626	PDLIM7
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6	485118	693161	EXOC2
6	3000047	3020017	NQO2
6	7281263	7313561	SSR1
6	8073573	8102848	EEF1E1
6	10695160	10710035	PAK1IP1

6	12012704	12212290	HIVEP1
6	13574486	13615410	SIRT5
6	13612511	13633109	NOL7
6	13621710	13711816	RANBP9
6	16299323	16761741	ATXN1
6	17600498	17611970	FAM8A1
6	24705069	24721084	C6orf62
6	26104156	26104585	HIST1H4C
6	26124350	26139357	HIST1H2AC
6	31078980	31080352	C6orf15
6	31830949	31846843	SLC44A4
6	32152490	32157983	PBX2
6	32808474	32812732	PSMB8
6	33244897	33246622	B3GALT4
6	33267451	33282184	TAPBP
6	33286315	33290813	DAXX
6	34555045	34664645	C6orf106
6	34857018	35085822	ANKS1A
6	36461646	36515276	STK38
6	42931591	42947001	PEX6
6	44213883	44221645	HSP90AB1
6	71377454	71571738	SMAP1
6	73951017	74019958	KHDC1
6	74078258	74079535	OOEP
6	74171434	74211199	MTO1
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6	83920088	84140958	ME1
6	86317482	86353588	SYNCRIP
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6	108881006	109005992	FOXO3
6	110501604	110553443	CDC40
6	111981515	112194675	FYN
6	112429114	112575944	LAMA4
6	116892563	116914458	RWDD1
6	118228669	118638859	SLC35F1
6	129204266	129837731	LAMA2
6	131160467	131384482	EPB41L2
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6	134490364	134639216	SGK1
6	137518601	137541001	IFNGR1
6	149068043	149398146	UST
6	149915989	149970174	KATNA1
6	150045437	150067708	NUP43
6	153332006	153452409	RGS17
6	158653248	158932880	TULP4
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6	159057486	159065824	DYNLT1
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6	160100128	160114373	SOD2
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6	170884640	170893800	PDCD2
7	1855408	2272603	MAD1L1

7	5566759	5570252	ACTB
7	6414106	6443618	RAC1
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7	16639381	16685462	ANKMY2
7	16793331	16824181	TSPAN13
7	20821874	20826528	SP8
7	23221426	23240650	NUPL2
7	23221426	23240650	NUPL2
7	26191827	26226777	NFE2L3
7	27778972	27869406	TAX1BP1
7	32524925	32534890	LSM5
7	37945514	37956545	SFRP4
7	38217788	38270292	STARD3NL
7	45139679	45151366	TBRG4
7	45951824	45960891	IGFBP3
7	45951824	45960891	IGFBP3
7	55538283	55640220	VOPP1
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7	66093848	66113984	KCTD7
7	66147131	66276471	RABGEF1
7	69063885	70257905	AUTS2
7	72716493	72722884	NSUN5
7	73150404	73153210	ABHD11
7	73703785	73820293	CLIP2
7	73868100	74016951	GTF2IRD1
7	74210463	74267892	GTF2IRD2
7	75162599	75368310	HIP1
7	75508297	75518264	RHBDD2
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7	75931855	75933634	HSPB1
7	80371834	80551715	SEMA3C
7	89975321	90020789	GTPBP10
7	92190052	92219726	FAM133B
7	94214516	94285541	SGCE
7	95034154	95064656	PON2
7	97481409	97501874	ASNS
7	99055764	99063844	ATP5J2
7	99055764	99063844	ATP5J2
7	99955606	99965474	PILRB
7	100171614	100183826	LRCH4
7	100797665	100804577	AP1S1
7	101459164	101927270	CUX1
7	102952901	102985340	DNAJC2
7	104754028	105039634	SRPK2
7	107204382	107218988	DUS4L
7	108110846	108168625	PNPLA8
7	120988885	121036442	FAM3C
7	127950409	127983982	RBM28
7	134127087	134143908	AKR1B1
7	135046527	135194895	CNOT4
7	138145059	138270353	TRIM24
7	138728246	138794486	ZC3HAV1
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7	139723524	139764106	PARP12
7	140033532	140104044	SLC37A3
7	141251058	141354229	AGK
7	143078318	143088224	ZYX
7	150076386	150095739	ZNF775
7	150755279	150773634	SLC4A2

7	150773688	150777990	FASTK
7	151253180	151574336	PRKAG2
7	156931635	157062086	UBE3C
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7	157129672	157210153	DNAJB6
8	11700013	11725666	CTSB
8	12039593	12051644	FAM86B1
8	13424332	13425817	C8orf48
8	21964363	21966952	NUDT18
8	23048950	23082700	TNFRSF10A
8	26239874	26270664	BNIP3L
8	27491080	27534306	SCARA3
8	27950564	28048690	ELP3
8	28351702	28431805	FZD3
8	28747891	28922476	HMBOX1
8	28747891	28922476	HMBOX1
8	29190559	29208287	DUSP4
8	30890758	31031297	WRN
8	33405252	33424666	RNF122
8	37716445	37757035	RAB11FIP1
8	37962463	37997618	ASH2L
8	38088841	38120371	DDHD2
8	38585684	38710566	TACC1
8	42995572	43057990	HGSNAT
8	61429449	61536223	RAB2A
8	67955294	67974582	COPS5
8	70584090	70747319	SLCO5A1
8	74206817	74237540	RDH10
8	74888357	74895038	TMEM70
8	82569131	82599049	IMPA1
8	86019303	86058335	LRRCC1
8	90769315	90803312	RIPK2
8	92261488	92410398	SLC26A7
8	92967175	93115474	RUNX1T1
8	97274147	97346794	PTDSS1
8	98787789	98864850	LAPTM4B
8	98881264	99048968	MATN2
8	100025279	100890467	VPS13B
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8	117858153	117887125	RAD21
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8	118811582	119124078	EXT1
8	120428532	120436698	NOV
8	124332070	124408725	ATAD2
8	130851819	131028917	FAM49B
8	132916336	133025909	EFR3A
8	145699095	145701738	FOXH1
8	146277803	146281436	C8orf33
9	2015322	2193644	SMARCA2
9	3824108	4300056	GLIS3
9	6010999	6015660	RANBP6
9	6413131	6507074	UHRF2
9	19115739	19127624	PLIN2
9	19376233	19380292	RPS6
9	21967731	21994510	CDKN2A
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9	26903348	26947488	PLAA
9	27109127	27230192	TEK
9	27546523	27573884	C9orf72

9	32553504	32573202	NDUFB6
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9	38392641	38398682	ALDH1B1
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9	73143959	74061802	TRPM3
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9	89559257	89562124	GAS1
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9	99075699	99146012	SLC35D2
9	100818939	100845385	NANS
9	103064337	103115876	TEX10
9	112137954	112260613	PTPN3
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9	114122953	114247045	KIAA0368
9	114311982	114362155	PTGR1
9	116037894	116056099	PRPF4
9	117781834	117880556	TNC
9	123151127	123342468	CDK5RAP2
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9	125132789	125158002	PTGS1
9	125329807	125330776	OR1L8
9	130209933	130213731	RPL12
9	130628739	130640042	AK1
9	130830459	130871557	SLC25A25
9	130922519	130926227	C9orf16
9	131071376	131084717	TRUB2
9	131937811	131940560	IER5L
9	133320074	133376681	ASS1
9	134165049	134184669	PPAPDC3
9	134165049	134184669	PPAPDC3
9	134452137	134615384	RAPGEF1
9	134735477	134955294	MED27
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9	136228305	136244840	SURF4
9	140083009	140084842	SSNA1
9	140317827	140328878	NOXA1
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10	5090938	5149898	AKR1C3
10	5903573	5931880	ANKRD16
10	7830073	7849784	ATP5C1
10	13319776	13342153	PHYH
10	16632595	16859529	RSU1
10	23728178	23731330	OTUD1
10	27399020	27443369	YME1L1
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10	33189226	33247313	ITGB1
10	33466399	33623853	NRP1
10	35927157	35930382	FZD8
10	38383244	38412300	ZNF37A
10	43084512	43134036	ZNF33B
10	44101835	44113372	ZNF485
10	45471689	45474350	C10orf10
10	51592060	51623406	TIMM23
10	61410502	61469669	SLC16A9
10	69556407	69597957	DNAJC12
10	70100844	70167071	RUFY2

10	71029720	71161658	HK1
10	71962566	71993687	PPA1
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10	79793498	79816591	RPS24
10	80828731	81076305	ZMIZ1
10	88809939	88854796	GLUD1
10	90973306	91011680	LIPA
10	91152283	91166264	IFIT1
10	93169017	93274606	HECTD2
10	93666325	93669278	FGFBP3
10	95066166	95242210	MYOF
10	97889452	97923537	ZNF518A
10	98277847	98346829	TM9SF3
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10	102737559	102747292	MRPL43
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10	104162354	104179711	PSD
10	105036899	105050128	INA
10	105206523	105212182	CALHM2
10	105353764	105615215	SH3PXD2A
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10	126085852	126107565	OAT
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11	644205	695760	DEAF1
11	790455	798289	SLC25A22
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11	1968482	2007315	MRPL23
11	2421703	2425128	TSSC4
11	3876913	4114460	STIM1
11	6642536	6685340	DCHS1
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11	27062232	27149374	BBOX1
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11	27676420	27743625	BDNF
11	32914772	33001836	QSER1
11	33106110	33183057	CSTF3
11	34073210	34124177	CAPRIN1
11	35160397	35253969	CD44
11	35639715	35642441	FJX1
11	43702088	43878189	HSD17B12
11	46765064	46867879	CKAP5
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11	62475046	62476698	GNG3
11	62480077	62494877	HNRNPUL2

11	62559577	62572984	NXF1
11	62574312	62599583	STX5
11	63742059	63744035	COX8A
11	63753305	63765912	OTUB1
11	63997574	64001773	DNAJC4
11	64126605	64139707	RPS6KA4
11	64532056	64546535	SF1
11	64879306	64883727	TM7SF2
11	65306010	65325878	LTBP3
11	65343489	65360141	EHBP1L1
11	65360306	65363487	KCNK7
11	65601285	65621598	SNX32
11	65601285	65621598	SNX32
11	66202530	66206330	MRPL11
11	66247464	66277150	DPP3
11	66288834	66313729	ZDHHC24
11	66406068	66435876	RBM4
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11	67056742	67069975	ANKRD13D
11	67159403	67165903	RAD9A
11	67374303	67380032	NDUFV1
11	67922310	67981270	SUV420H1
11	68522068	68611898	CPT1A
11	68658724	68671323	MRPL21
11	71639748	71708663	RNF121
11	71900582	71907387	FOLR1
11	74971146	75062895	ARRB1
11	75526192	75855302	UVRAG
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11	76060984	76091900	PRKRIR
11	77589746	77705791	INTS4
11	85405244	85522217	SYTL2
11	88026740	88070961	CTSC
11	89933577	89956552	CHORDC1
11	93463348	93474723	TAF1D
11	94898657	94965725	SESN3
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11	102188161	102210154	BIRC3
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11	107992238	108018915	ACAT1
11	108028097	108093385	NPAT
11	111652899	111742325	ALG9
11	111797848	111893394	DIXDC1
11	114310088	114321021	REXO2
11	118967193	118973144	DPAGT1
11	119225905	119252456	USP2
11	120107329	120190673	POU2F3
11	120207244	120360665	ARHGEF12
11	121322892	121504491	SORL1
11	122526378	122685207	UBASH3B
11	122753216	122830450	C11orf63
11	125315621	125366226	FEZ1
11	125439278	125454595	EI24
11	125616160	125619763	PATE1
11	125763360	125773165	PUS3
12	3186501	3395750	TSPAN9
12	4382881	4414542	CCND2
12	6643565	6647557	GAPDH
12	6759684	6772331	ING4

12	6833130	6841061	COPS7A
12	7245980	7261889	C1RL
12	7341739	7371190	PEX5
12	7965090	8043812	SLC2A14
12	8798520	8815453	MFAP5
12	12878831	12944420	APOLD1
12	12966260	12982935	DDX47
12	22199088	22218628	CMAS
12	25358160	25403890	KRAS
12	28110997	28125684	PTHLH
12	29493559	29534163	ERGIC2
12	32832114	32898604	DNM1L
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17	78075319	78093700	GAA
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19	17830283	17845344	MAP1S
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22	20119344	20135550	ZDHHC8
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22	25348656	25593435	KIAA1671
22	26921694	26986109	TPST2
22	26921694	26986109	TPST2
22	29168642	29185303	CCDC117
22	29702965	29708798	GAS2L1
22	31058019	31063894	DUSP18
22	31500743	31503571	SELM
22	35653425	35691820	HMGXB4
22	36677303	36784127	MYH9
22	37865081	37882519	MFNG
22	38302135	38338485	MICALL1
22	38686677	38714109	CSNK1E
22	38864047	38879472	KDELR3
22	38864047	38879472	KDELR3
22	38879423	38903642	DDX17
22	39101713	39129612	GTPBP1
22	39257448	39268278	CBX6
22	39436589	39451997	APOBEC3F
22	39436589	39451997	APOBEC3F
22	40806272	41032710	MKL1
22	42017230	42060072	XRCC6
22	42069917	42085316	NHP2L1
22	42229063	42303332	SREBF2
22	42979707	43010988	POLDIP3
22	43013826	43045425	CYB5R3

22	43013826	43045425	CYB5R3
22	43192510	43253428	ARFGAP3
22	46316226	46373028	WNT7B
22	46731278	46753257	TRMU
22	51017367	51021448	CHKB
22	51061162	51066621	ARSA
22	51113050	51171660	SHANK3